



A case of brainstem encephalitis treated with plasmapheresis

Plasmapheresis treatment for brainstem encephalitis

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Abstract

Brain stem encephalitis is a rare disease, which can be triggered by infection, with an unclear etiology, in which infectious and autoimmune mechanisms are thought to play a role in the pathogenesis [1]. Major clinical symptoms are ataxia, muscle weakness and ocular and bulbar dysfunction [2]. Its etiology can vary from infection to autoimmune reasons. Listeria, enterovirus type 71 and Herpes simplex virus are the most common infectious causes. It may also be caused by neurobehçets, Bickerstaff's encephalitis, autoimmune diseases such as multiple sclerosis and paraneoplastic reasons [3-5]. With those in mind, the underlying etiology is unclear in most cases [2]. Treatment is based on etiology. Immunosuppressive treatment can be tried in brain stem encephalitis patients whose etiology can not be made clear [6]. In this case report, we present a case of brainstem encephalitis which did not respond to the present treatment and was treated with plasmapheresis.

Keywords

Brain Stem Encephalitis; Plasmapheresis

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Case Report

The otherwise healthy 16-year-old girl was admitted to an outer center with fever, vomiting, and diarrhea seven days ago. Antibiotherapy and supportive therapies were given to the patient. There were no characteristics in the history of the patient who applied to our hospital due to headache, double vision and unbalanced gait joined her list of complaints. On physical examination, consciousness was present, Glasgow coma score was (GCS): 15, body temperature was: 38.9 °C, nuchal stiffness, left eye outward gaze restriction and bilateral papillary stasis was present, deep tendon reflexes were normoactive, muscle strength in lower and upper extremities were 5/5, and there was no pathological reflex. Laboratory studies showed, WBC: 11000 / mm³, Hb: 13,6 gr / dL, platelet count: 424,000 / mm³, erythrocyte sedimentation rate (ESR): 3 mm / h, procalcitonin: 0.089 ng / mL, renal and liver functions normal, serum sodium: 132 mg / dL, potassium: 3.9 mg / dL. Contrast-enhanced brain magnetic resonance imaging (MRI) revealed findings consistent with leptomeningeal involvement and pathological signal enhancement at the brainstem level (Figure 1). The patient was admitted to pediatric infection

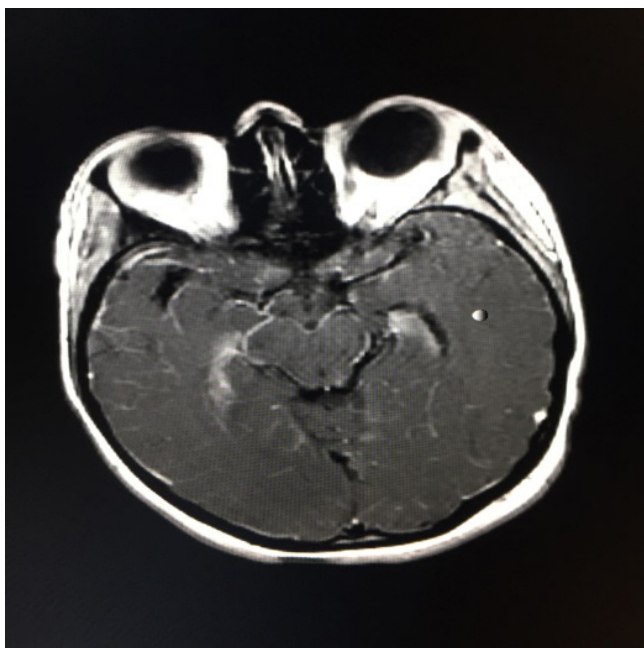


Figure 1. Cranial MRI axial contrast-enhanced T1-section: Increased leptomeningeal contrast enhancement predominantly in both cranial basal cisterna but also in infratentorial and supratentorial levels.

service with an initial diagnosis of meningitis, encephalitis, and a lumbar puncture was done. Lumbar puncture results were as follows: Cerebrospinal fluid (CSF) protein: 258 mg / dL, glucose: 37 mg / dL, concurrent blood glucose: 95 mg / dL, CSF pressure: 47 cmH₂O. Treatment with ceftriaxone, vancomycin, and acyclovir was started in patients with abundant lymphocytes presenting direct examination on CSF. Etiologic examinations included: Serum salmonella, brucella, measles, varicella, mumps, borrelia, chlamydia, mycoplasma, Epstein-Barr virus, toxoplasmosis, cytomegalovirus serologies, which all came back negative; ANA, Anti-DNA and otoimmune panel were negative; complement C3, C4 immunoglobulin, and immunodeficiency panel were in normal range by age; antithyroglobulin antibodies and antimicrosomal antibodies were negative for Hashimoto's encephalitis; thyroid function tests were normal; lactic acid and pyruvic acid for metabolic disease were normal; CSF was negative for tuberculosis PCR, ARB, MGIT, Herpes PCR and

brucella; no growth was observed in blood, urine and CSF cultures. ARB and MGIT in the fasting stomach fluid were negative, tuberculin skin test was anergic, and Quantiferon assay was unspecified. The patient was transferred to our child intensive care unit on the 10th day of treatment with generalized tonic-clonic seizures, developed speech difficulty and neurologically worsening condition. Intravenous levetiracetam was loaded and continued with the maintenance dose. EEG showed no active epileptic activity, but a mild base arrhythmia was present. Patients physical examination results were; blood pressure: 100/70 mmHg, heart rate: 120/min, neurological examination results were; Glasgow coma scale: 10, deep tendon reflexes not present, muscle strength was 3/5 on the upper and lower extremities, bilateral papillae stasis and bilateral abducens paralysis was present and gag reflex was poor. There was no hemorrhage or edema in the immediate non-contrast brain tomography. Cerebral salt wasting was considered in the patient with a serum sodium of 120 mg / dL, urine sodium of 263 mg / dL, urine density of 1017, urine osmolality of 600 mOsm / liter, serum osmolality of 256 mOsm / liter and urine output of 8 mL/kg. The patient was supplemented with 3% hypertonic saline solution. When the response to the fluid treatment was not sufficient, fludrocortisone was added to the treatment. On the fourth day of intensive care unit admission, the patient was intubated, and invasive mechanical ventilation was performed with neurologically worsening condition with right central facial paralysis, 6th, 7th, 9th, and 10th cranial nerve involvement and gag, and airway reflexes were not present. In repeated contrast cranial MRI, supratentorial and infratentorial leptomeningeal contrast enhancement around the basal cistern, and a slight increase in the ventricular system width compared to the previous MRI were detected. Passive physical therapy exercises were started to the patient whose electromyographic examination revealed sensory nerve conduction to be normal, motor nerve conduction to be normal at the upper body half, a bilateral lower fibular nerve neuropathy and a drop foot. The patient regained consciousness but was quadri-paralysed and had ophthalmoplegia, lateral gaze palsy, areflexia and no gag reflex. The patient could not pass the spontaneous breathing trials and could not tolerate extubation. With the clinical and radiological findings, brain stem encephalitis was suspected in the patient. The patient was given 2 g / kg IVIG over four days. In the absence of clinical improvement, the patient underwent plasmapheresis. Plasmapheresis was performed in a pediatric intensive care unit with the Spectra Optia® (Terumo BCT, Lakewood, CO) apheresis device with a 12 Fr hemodialysis catheter placed in the internal jugular vein for five days in a row and 2 sessions on alternate days. The patient's total blood volume was 3951 mL, total plasma volume was 2906 mL. Fresh frozen plasma was used as replica liquid in all treatments. Anticoagulation was achieved with ACD-A (Acid Citrate Dextrose-formulas) alone. A mean of 4219 mL (min:2270 mL-max:5109 mL) of blood was processed in the procedures, with an average of 2532 mL (min:1328 mL - max:3184 mL) replicates (Replacement per kilogram: average 42 mL / kg, min: 22 mL / kg-max: 52 mL / kg). The mean total blood flow rate was 45.2 mL / min (min:35 mL/minutes-max:50 mL/minutes). Processes lasted an average of 95.2 min (min: 54 min-max: 112 min). In all procedures, intravenous calcium replacement was performed at a dose appropriate to the patient's body weight. In one procedure, the patient developed severe urticaria. The patient was administered antihistamines, but the procedure was

terminated because there was no regression in the symptoms. Control post-treatment cranial MRI showed leptomeningeal contrast enhancement and hydrocephalic regression. At the follow-up, the mechanical ventilator support was reduced, and the patient was excused. The patient was transferred to the clinic during the third week of intensive care. The patient was discharged on the 32nd day of hospitalization. There was a regression in the present findings in MRI taken at two months after treatment (Figure-2).

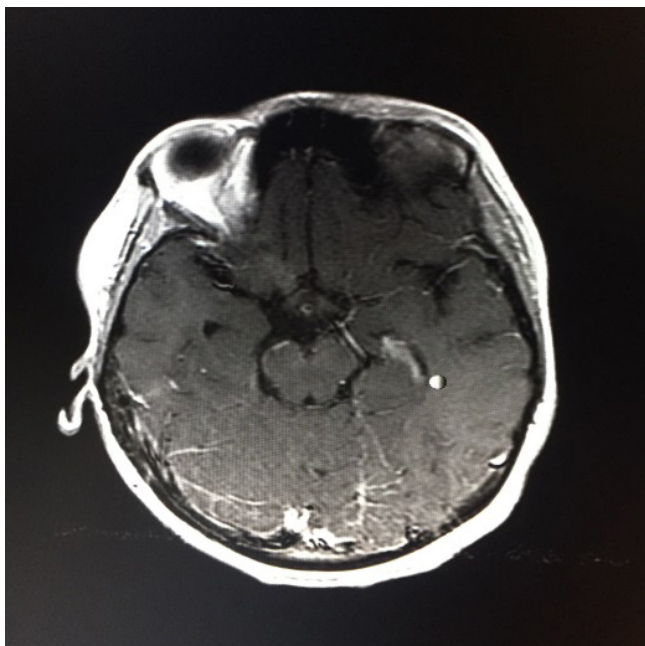


Figure 2. Significantly decreased contrast enhancement at the same site in control cranial MRI at two months after treatment.

Discussion

Brainstem encephalitis is a rare clinical entity. Infection, autoimmune diseases, and paraneoplastic syndromes play a role in its etiology. With *Listeria*, enterovirus type 71, herpes simplex virus on top, trigger infections include; cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, measles virus, *Brucella*, salmonella, tuberculosis, aspergillosis, *Borrelia*, mycoplasma and *Campylobacter jejuni*. Neurobehçet's disease, neurosarcoidosis, Bickerstaff's encephalitis, Hashimoto's encephalitis, Susac's syndrome, Multiple sclerosis, systemic lupus erythematosus, and polychondritis are among autoimmune diseases associated with brain stem encephalitis [3]. In the case of Bickerstaff's encephalitis, serum anti-GQ1b antibodies are generally positive, but negativity does not exclude the diagnosis [7]. In our case, the anti-GQ1b antibody level could not be studied. Another etiology, paraneoplastic syndromes, is frequently associated with anti-Yo, anti-Tr, anti-Hu, and anti-Ma antibodies. However, in most cases, no etiology can be detected as it is in our case [6].

In most cases, there is a respiratory or gastrointestinal system complaint about 7-10 days before the development of brainstem dysfunction [1]. In our case, a history of vomiting, complaints of diarrhea and treatment in an external center a week ago was present. Approximately 75% of patients have cranial nerve involvement. Cerebellar ataxia is more frequent in infectious and paraneoplastic etiologic brain stem encephalitis cases [8]. Ataxia was the presenting symptom in our case, and 6th, 7th, 9th and 10th cranial nerve involvement has developed in the follow-up.

For the etiologic diagnosis, MRI is very important. The most

common MRI findings are increased signal in the pons, medulla oblongata and cerebellum on T2 weighted and FLAIR MRI sections. Although there are mainly infratentorial lesions in *Listeria* infection and Behçet's disease, both infratentorial and supratentorial involvement are present in multiple sclerosis [6,9]. MRI is normal in cases of paraneoplastic etiologic brainstem encephalitis. There was both infratentorial and supratentorial involvement around the basal cistern at the time of MRI. With these radiological findings, autoimmune ground brainstem encephalitis was considered in our patient. In addition to diagnosis, MRI is also used for treatment response and clinical follow-up.

Serological and immunologic tests for infectious, autoimmune, and paraneoplastic causes, as well as brain biopsy, can be used for diagnosis [10]. Tan et al. in their study of 81 brainstem encephalitis patients between 1.5 and 72 years of age, 14 of the patients were diagnosed with brain biopsy. Biopsies were made of the brain stem, cerebellum, cerebellum, and thalamus. Only one patient developed dysarthria after brain biopsy, and no mortality associated with brain biopsy was reported [2]. We did not perform brain biopsy in our case.

The treatment is planned according to etiology. Appropriate antimicrobial therapy is used in the treatment of the infectious group. Because *Listeria* and herpes simplex virus are the most frequently treatable infectious agents, empirical treatment of ampicillin and acyclovir is generally initiated. In the autoimmune group, corticosteroids are used as first-line treatment. Plasmapheresis, intravenous immunoglobulin, cyclophosphamide, mycophenolate mofetil are used as second-line immunotherapies in patients with inadequate response to steroids [2,11]. Study of Tan et al. have shown that brainstem encephalitis with undetectable etiology is highly likely to have an autoimmune base and that this group has benefited strongly from immunosuppressive therapies. Empirically, immunotherapy is recommended in patients with brainstem encephalitis with undefined etiology and who have no spontaneous regression or progression with clinical and radiological progression [2]. Prytula et al. reported good clinical results in five patients with plasmapheresis in a series composed of 8 patients diagnosed with transverse myelitis, Bickerstaff brainstem encephalitis, paraneoplastic encephalitis, unidentified etiology encephalitis and neuromyelitis optica, age between 2-12, and the effectiveness of plasmapheresis has been noted in autoimmune-mediated central nervous system diseases [12]. Odaka et al. reported that they used steroids, IVIG and plasmapheresis alone or combined in treatment in a series of 62 Bickerstaff brachial encephalitis aged between 3 and 91 years [13]. In our case, IVIG treatment for four days with 2 gr/kg, followed by 7 sessions of plasmapheresis resulted in uneventful recovery. In our case, the etiology could not be determined, and the case which did not resolve with IVIG treatment was treated with plasmapheresis.

The cerebral salt loss is one of the most common causes of hypovolemic hyponatremia. It can be seen in the course of head trauma, intracranial infections, and masses. It is a transient phenomenon that generally improves within three weeks [13]. Proper fluid and fludrocortisone are used in treatment. Fludrocortisone acts directly on the renal tubules to reduce sodium excretion, thus avoiding negative salt balance [14]. In our case, the patient was admitted to pediatric intensive care unit, and hypertonic liquid and fludrocortisone treatment were applied, after hyponatremic convulsion due to cerebral salt loss. In our PubMed-based literature review, Vega et al. reported

a 52-year-old woman with cerebral salt loss due to *Listeria rhombencephalitis*, but we could not find a case of brainstem encephalitis and cerebral salt loss associated with pediatric age group [15].

In conclusion, plasmapheresis therapy should be kept in mind in cases of pediatric patients with brain stem encephalitis which does not respond to current treatments.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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